Solid-Phase Synthesis of 1,3,6-Trisubstituted-1*H*-thiazolo[4,5-*c*][1,2]thiazin-4(3*H*)one-2,2-dioxide Derivatives using Traceless Linker

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A new solid-phase route for preparation of 1,3,6-trisubstituted-1*H*-thiazolo[4,5-*c*][1,2]thiazin-4(3*H*)one-2,2-dioxide derivatives is described. Our synthetic route is begun with a thiazole resin and relies on the sulfonamide formation, Mitsunobu-type N-alkylation, cyclization, and nucleophilic substitution methodology cleavage on a solid support. The strategy permits the incorporation of three points of diversity into the thiazolo[4,5-*c*][1,2]thiazine ring system in good overall yields.

Introduction

Combinatorial chemistry of small organic molecules in solution phase or on solid support has a significant impact on the drug discovery[1,2] Among organic small molecules, heterocyclic compounds have received particular attention in combinatorial chemistry because they are important structural components of bioactive molecules.[2] In this regard, because the thiazole and thiazine derivatives exhibit a wide range of important biological activities,[3] they serve as attractive targets for combinatorial library construction via solid-phase synthesis. For example, thiazoles exhibits the activities against cyclin-dependent kinase (CDK)[3a] and glycogen synthase kinase-3 (GSK-3).[3b] Thiazines compounds are active as NMDA receptor glycine site antagonist[3c] and as kinase inhibitors in the treatment of hyperproliferatives diseases.[3d]

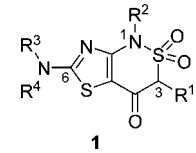
The synthetic methods for the various fused-thiazine compounds has been well documented, including thieno[3,2-*c*][1,2]thiazin-4-one and pyrazolo[3,4-*c*][1,2]thiazin-4-one.[4] However, as far as we know, there is no report which describes the synthesis of thiazolo[4,5-*c*][1,2]thiazine derivatives and routes to five-membered ring fused-[1,2]thiazines on solid-phase.

Previously, we already described a facile and rapid solid-phase strategy for the preparation of a small molecule library based on the thiazole scaffold using a traceless linker.[5] As part of a recent drug discovery project, we required concise solid- or solution-phase methods to construct a fused-thiazolo heterocycle library. Herein, we report our recent progress on this project, which includes the first solid-phase synthetic protocol for 1,3,6-trisubstituted-1*H*-thiazolo[4,5-*c*][1,2]thiazin-4(3*H*)one-2,2-dioxide derivatives **1** (Figure 1). We believe our efficient approach is suitable for the construction of druglike compound libraries in a high-throughput manner.

Results and Discussion

The initial solid phase synthetic route we developed for preparation of substances containing the thiazole scaffold[5] involved the formation of the intermediate thiazole resin **2** from solid supported cyanocarbonimidodithioate **4**, which is derived from the Merrifield resin **3** and dipotassium cyanodithioimidocarbonate[6] (Scheme 1). Treatment of **4** with ethyl 2-bromoacetate (**5**), followed by cyclization produces the solid-phase bound thiazole **2**.

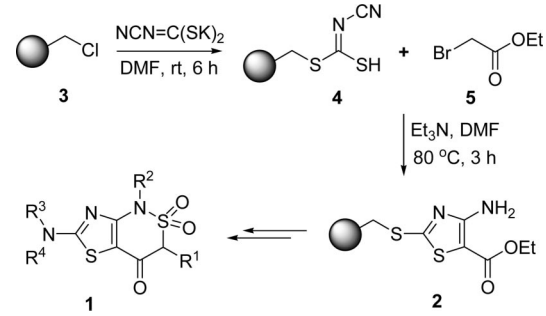
With large quantities of resin **2** in hand, the stage was set for exploration of procedures needed to transform the



1

Figure 1. Structure of 1,3,6-trisubstituted-1*H*-thiazolo[4,5-*c*][1,2]thiazin-4(3*H*)one-2,2-dioxide (**1**).

Scheme 1. Solid-Phase Synthesis of Thiazole Amino Ester Resin **2** As Key Intermediate



3 **4** **5** **1** **2**

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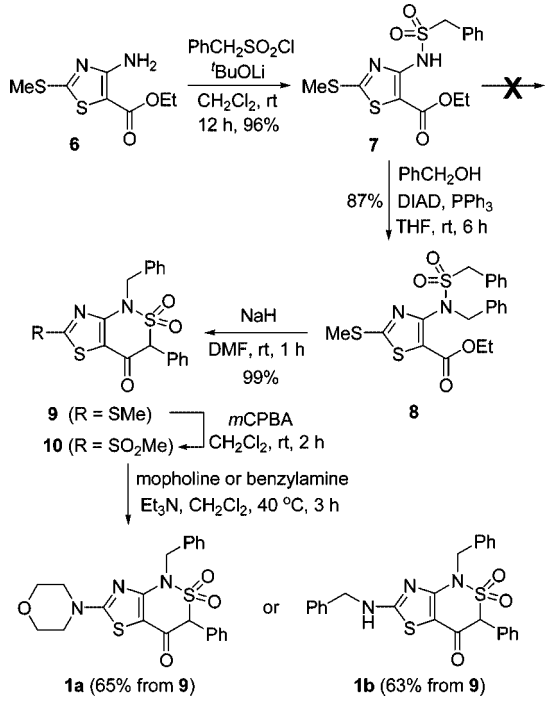
Scheme 2. Solution-Phase Synthesis of the Thiazolo[4,5-*c*][1,2]thiazines **1a** and **1b**



thiazole amino ester resin **2** to the corresponding thiazolo[4,5-*c*][1,2]thiazine derivatives **1** (Scheme 2). The solution-phase chemistry of the known thiazole amino ester **6**[7] was probed as a model for developing optimal processes and conditions. This ester was converted to the corresponding sulfonamide **7** via reaction with sulfonyl chloride. Initial attempts to N-sulfonylate this substance with benzylsulfonyl chloride in the presence of either Et_3N, pyridine, or KHMDS did not bring about complete conversion, even when reflux conditions and various solvents (CH_2Cl_2, MeCN, and THF) were used. In contrast, the N-sulfonylation of **6** with benzylsulfonyl chloride takes place efficiently when ^{t}BuOLi is used as the base (12 h at room temperature) and CH_2Cl_2 as the solvent. Under these conditions, the *N*-benzylsulfonamide derivative **7** is generated in high yield (96%).

Attempts to promote cyclization of the sulfonamide **7** to form the corresponding thiazolo[4,5-*c*][1,2]thiazine using a number of reaction conditions (NaH/THF or DMF,[4,8] NaOEt/EtOH, and KHMDS/THF) were unsuccessful. For the synthesis of the thiazolo[4,5-*c*][1,2]thiazine ring system, we modified the reaction sequence deliver the thiazolo[4,5-*c*][1,2]thiazine ring product in good overall yield (86%). After N-alkylation of **7** with benzyl alcohol (one possible diversity element) under Mitsunobu conditions (DIAD/PPh_3)[8a,9] the sulfonamide derivative **8** was produced, which undergoes cyclization (NaH/THF) to form the thiazolo[4,5-*c*][1,2]thiazine **9**. Although thiazolo[4,5-*c*][1,2]thiazine **9** is capable of existing in two tautomeric forms (Figure 2), only the keto-form is detected using NMR spectroscopy. The H-3 proton peak in the ^{1}H NMR spectrum of **9** resonates at 5.09 ppm, and in the ^{13}C NMR, the C-4 carbonyl and the methine C-3 carbons appear at 179.4

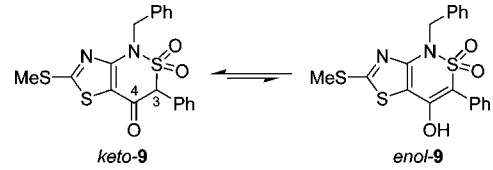
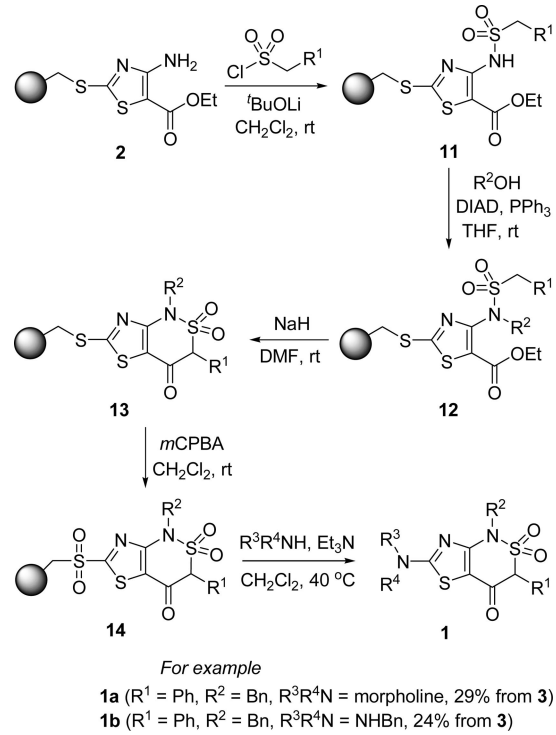


Figure 2. Tautomeric equilibrium of thiazolo[4,5-*c*][1,2]thiazine **9**.

Scheme 3. Solid-Phase Synthesis of Thiazolo[4,5-*c*][1,2]thiazine Derivatives **1**



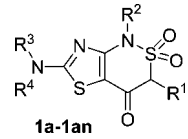
and 75.1 ppm, respectively. These NMR chemical shifts are consistent with predicted values for the keto-form.

Following conversion of **9** to sulfone **10** (*m*CPBA/CH_2Cl_2) substitution reactions promoted by treatment with morpholine and benzylamine in CH_2Cl_2 furnished the respective thiazolo[4,5-*c*][1,2]thiazine derivatives **1a** (65%) and **1b** (63%). The products **1a** and **1b** were fully characterized using ESI-LC-MS, as well as ^{1}H and ^{13}C NMR methods. The results of this study show that an efficient solution-phase synthetic route is available for conversion of the model thiazole amino ester **6** to the thiazolo[4,5-*c*][1,2]thiazines **1**.

On the basis of these successful solution-phase reaction conditions, the solid-phase synthesis of thiazolo[4,5-*c*][1,2]thiazines introduces diversity elements via selection of the sulfonyl chloride, alcohol, and amine building blocks (Scheme 3). The synthetic route began with thiazole amino ester resin **2** (see Scheme 1), which was obtained starting with Merrifield resin **3** by using the previously described procedure.[5]

Resin **2** was first swollen in CH_2Cl_2, and in a manner that parallels the route employed in the solution-phase synthesis, it was reacted with a selected benzylsulfonyl chloride to give the corresponding sulfonamide resin **11**, potentially containing the first diversity element R^1. The progress of this reaction (R^1 = Ph) was monitored by

Table 1. Solid-Phase Synthesis of Thiazolo[4,5-*c*][1,2]thiazines **1**[a]



1a-1an

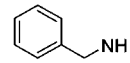
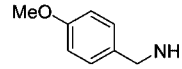
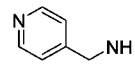
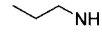
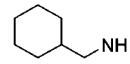
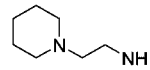
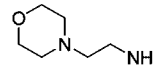
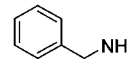
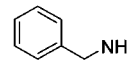
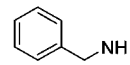
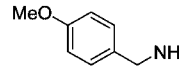
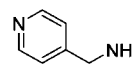
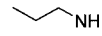
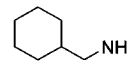
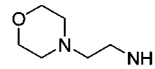
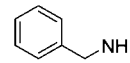
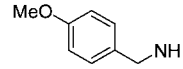
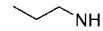
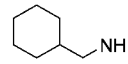
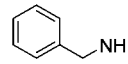
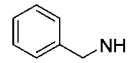
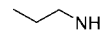
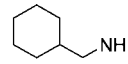
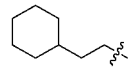
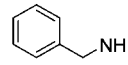
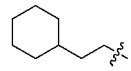
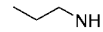
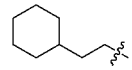
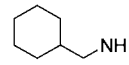
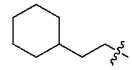
Entry	Compound	R^1	R^2	R^3R^4N	Yield (%)[b]	Purity (%)[c]
1	**1a**	Ph	Bn		29	99
2	**1b**	Ph	Bn		24	99
3	**1c**	Ph	Bn		22	99
4	**1d**	Ph	Bn		16	99
5	**1e**	Ph	Bn		22	99
6	**1f**	Ph	Bn		20	98
7	**1g**	Ph	Bn		19	96
8	**1h**	Ph	Bn		20	98
9	**1i**	Ph	Bn		19	99
10	**1j**	Ph	Bn		18	98
11	**1k**	Ph	Bn		19	97
12	**1l**	H	Bn		N.C.[d]	-
13	**1m**	H	Bn		N.C.[d]	-
14	**1n**	Et	Bn		N.C.[d]	-
15	**1o**	Et	Bn		N.C.[d]	-
16	**1p**	Ph	4-MeO-Bn		18	99
17	**1q**	Ph	4-MeO-Bn		18	99
18	**1r**	Ph	4-MeO-Bn		17	98
19	**1s**	Ph	4-MeO-Bn		17	98
20	**1t**	Ph	4-MeO-Bn		18	99
21	**1u**	Ph	4-MeO-Bn		22	99
22	**1v**	Ph	4-MeO-Bn		16	97
23	**1w**	Ph	4-MeO-Bn		21	99

Table 1. Continued

Entry	Compound	R^1	R^2	R^3R^4N	Yield (%)[b]	Purity (%)[c]
24	**1x**	Ph	4-MeO-Bn		20	99
25	**1y**	Ph	4-Me-Bn		28	99
26	**1z**	Ph	4-Me-Bn		23	97
27	**1aa**	Ph	4-Me-Bn		23	98
28	**1ab**	Ph	4-Me-Bn		22	97
29	**1ac**	Ph	4-Me-Bn		19	98
30	**1ad**	Ph	4-Me-Bn		20	97
31	**1ae**	Ph	4-NO_2-Bn		N.R.[e]	-
32	**1af**	Ph	4-NO_2-Bn		N.R.[e]	-
33	**1ag**	Ph	Et		21	99
34	**1ah**	Ph	Et		19	99
35	**1ai**	Ph	Et		18	98
36	**1aj**	Ph	Et		17	99
37	**1ak**	Ph			11	99
38	**1al**	Ph			13	99
39	**1am**	Ph			12	96
40	**1an**	Ph			12	98

[a] All reactions were performed on a 150−200 mg scale of resin **14**. [b] Seven-step overall isolated yield from Merrifield resin **3** (loading capacity = 0.94 mmol/g). [c] Determimed on the basis of LC/MS spectrum (integration of diode array 200−400 nm traces) of isolated product. [d] Not completed and obtained noncyclized product in about 20% yield. [e] No reaction and decomposed.

ATR-FTIR spectroscopy (Figure 3), which showed the disappearance of the NH_2 band at 3493 and 3363 cm^{-1} and a shift of the ester band from 1666 to 1673 cm^{-1}. The sulfonamide resin **11** was then reacted under Mitsunobu conditions with a benzyl alcohol (PPh_3, DIAD, THF, room temperature). The progress of this process, which efficiently produced resin **12** (R^1 = Ph, R^2 = Bn) and introduced the second potential diversity element R^2, was monitored by using ATR-FTIR (ester band at 1705 cm^{-1}). Cyclization reaction of resin **12** was promoted by NaH/DMF and led to formation of the desired thiazolo[4,5-*c*][1,2]thiazine containing resin **13** (R^1 = Ph, R^2 = Bn), a reaction also monitored by the characteristic disappearance of the ester at 1705 cm^{-1} and concurrent formation of the ketone band at 1661 cm^{-1}. Treatment of resin **13** with *m*CPBA in CH_2Cl_2 led to generation of the resin bound cyclic sulfonamide **14**. Although this reaction is not amenable to ATR-FTIR monitoring, solution-phase thiazole synthetic studies are well-known.[10]

Finally, the thiazolo[4,5-*c*][1,2]thiazine derivatives **1a** and **1b** were formed and cleaved from the resin (in a traceless manner) by treatment of resin **14** with morpholine and benzylamine in CH_2Cl_2, respectively, in respective yields of 29% and 24% over the seven step routes beginning with Merrifield resin **3**. The ^1H NMR spectroscopic properties of **1a** and **1b**, following purification by passing through a short plug of silica, were identical to

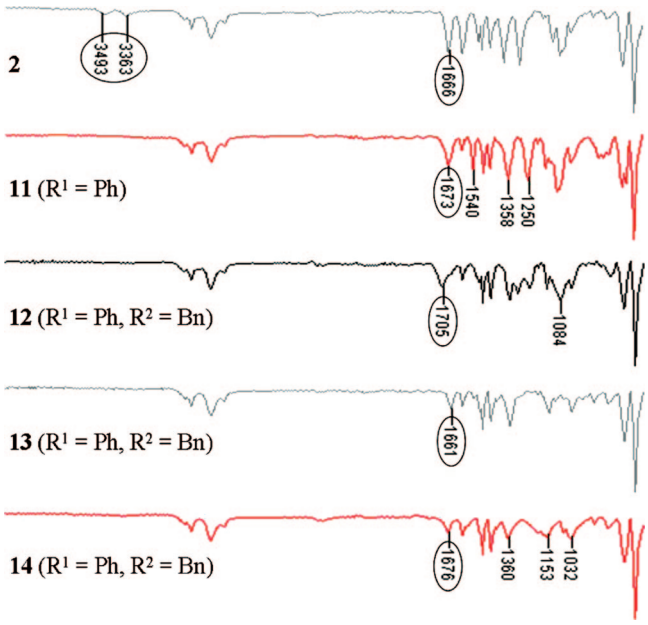


Figure 3. ATR-FTIR spectra of resins **2** and **11**−**14** (R^1 = Ph, R^2 = Bn).

the corresponding substances produced by using solution-phase synthetic routes.

By employing the new solid-phase synthetic route, we can prepare the thiazolo[4,5-*c*][1,2]thiazine derivatives **1** from Merrifield resin **3** and appropriate sulfonyl chloride ($R^1CH_2SO_2Cl$), alcohol (R^2OH), and amine (R^3R^4NH) starting materials. The substances generated in this way along with isolated yields by passing through a short plug of silica are given in Table 1.

When the R^1 in resin **12** is phenyl, the thiazolo[4,5-*c*][1,2]thiazines were obtained in good yields (Table 1, entries 1−11). However, reaction of intermediate resins **12** (R^1 = H or Et) under the optimal conditions failed to produce precursors of the respective target compounds **1l**−**1o** and only noncyclized products[11] were isolated in ~20% yield (entries 12−15). This problem is likely the consequence of the lower acidity of the C-3 α-protons in **12l**−**12o**.[12] The R^2 groups, introduced by using this sequence, are composed of benzyl moieties containing various electron-withdrawing and electron-donating constituents and two aliphatic moieties of differing steric bulk. In cases where the R^2 substituent is an electron-donating substituted benzyl or the simple ethyl moiety, the thiazolo[4,5-*c*][1,2]thiazine products **1** are formed in moderate yields (entries 16−24 for 4-MeO-Bn, entries 25−30 for 4-Me-Bn, and entries 33−36 for Et). In contrast, the sequence in which R^2 is an electron-withdrawing benzyl (4-NO_2-Bn) failed to produce the desired target (entries 31 and 32). It appears that the acidic proton present in **12** (R^2 = 4-NO_2-Bn) causes cyclization to produce **13** to be ineffective.[8a] In addition, in cases where R^2 is a bulky aliphatic group (e.g., 2-cyclohexyl-ethyl), the cyclization products are obtained in comparably lower yields (entries 37−40). Finally, the desulfonative nucleophilic substitution step takes place smoothly when various benzyl, primary aliphatic, and secondary amines are employed (entries 1−11).

In summary, the isolated yields for thiazolo[4,5-*c*][1,2]thiazines produced by using this solid-phase approach ranged from 11 to 29% for seven linear steps starting with Merrifield resin **3**, indicating that the average yield for each step of 73−84%. In addition, the thiazolo[4,5-*c*][1,2]thiazines were isolated in high purities (>95%) as judged from LC-MS and ^{1}H NMR analyses. This investigation, has led to the development of the first traceless solid phase route for the synthesis of 1,3,6-trisubstituted-1*H*-thiazolo[4,5-*c*][1,2]thiazin-4(3*H*)one-2,2-dioxide derivatives that contain three diversity positions. The strategy is based on an efficient solution-phase sequence, enables the construction of a library from an array of sulfonyl chlorides, alcohols, and amines.

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Supporting Information Available. Full experimental procedures and analytical data of compounds and copies of ^{1}H NMR and LC-MS spectrum of compounds **1a**−**1k**, **1p**−**1ad**, **1ag**−**1an**, **1′l**−**1′o**, and **7**−**9**, ^{13}C NMR spectrum of compounds **1a**, **1b**, and **7**−**9**, and ATR-FTIR spectra of resins **2**−**4** and **11**−**14**. This material is available free of charge via the Internet at http://pubs.acs.org.

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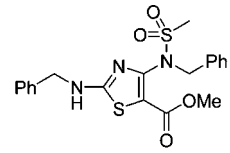
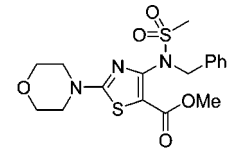
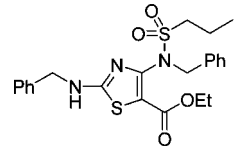
(11) When the reaction mixtures for the cyclization steps in the routes to **1l** and **1m** were quenched by addition of MeOH, the target products **1l** (Table 1, entry 12) and **1m** (entry 13) were obtained in 18% and 21% yields, respectively. In addition, in the cases using H_2O, the products **1′n** (23%, entry 12) and **1′o** (23%, entry 13) were obtained.



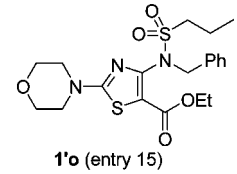
1'l (entry 12)



1'm (entry 13)



1'n (entry 14)



1'o (entry 15)

(12) The cases using various reaction conditions (for example, NaOEt/EtOH, LHMDS, or KHMDS/THF and *sec*-BuLi/THF) did not give the desired products.

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